REMARKS

Claims 1-12, 14-17 and 19-21 are pending in the application. In the Office Action mailed May 17, 2004, claims 1, 2, 6-12, 14-17 and 19-21 stood allowed and claims 3-5 were objected to for alleged informalities. However, in the present Office Action, claims 1-12, 14-17, and 19-21 are now rejected.

The amendments to the claims find support in the application as originally filed. The amendments to claims 1, 14, and 16 find support in the application at page 12, lines 24-26; page 20, lines 30-36; and elsewhere in the specification, figures, and claims as originally filed.

No new matter is added by way of the claim amendments.

Claims 1-8, 10, 12, 14-17, and 19-21 stand rejected under 35 U.S.C. §112, first paragraph. Claims 1, 3-8, 10, 12, 14, and 16 stand rejected under 35 U.S.C. §102(e). Claim 9 stands rejected under 35 U.S.C. §103(a).

Applicants respectfully traverse the claim rejections.

The Telephone Conversation with the Examiner

Applicants thank the Examiner for his clarification that the notice that claims 1-12, 14-17 and 19-21 were subject to a Restriction Requirement referred to the previously issued requirement, which had been properly responded to, and for his comments on the claim rejections during the telephone conversation of September 6, 2006.

The Patent Office Delay and Rescission of Allowance

Applicants respectfully object to the rejections of the claims "[u]pon further consideration," and further respectfully object to the apparently unreasonable delay (more than two years) between the response filed June 14, 2004 and the present action

issued on July 19, 2006 which gives an unexpected reversal of the claim allowances that were made previously by the U.S. Patent and Trademark Office.

Applicants note that "piece-meal" examination is to "be avoided as much as possible" (M.P.E.P. § 707.07(g)) and respectfully submit that such "piece-meal" examination is unwarranted in the present case. Applicants diligently and in good faith prosecuted the application to allowance of all but 3 of 19 pending claims (the 3 non-allowed claims were objected to only for matters of form). However, after a delay of more than two years, with no suggestion at any time until now that the claims would not be allowed, Applicants are now faced with a reversal of the U.S. Patent Office's position and with the rejection of all claims.

Applicants respectfully traverse the present rejections as inappropriate "piece-meal" examination and request their withdrawal.

The Requirement for Election/Restriction

The Office Action Summary of the Office Action mailed on July 19, 2006 indicates that claims 1-12, 14-17, and 19-21 are subject to restriction and/or election requirement. Pursuant to the Examiner's comments during a telephone conversation with the Applicants attorney, it is understood that no new restriction and/or election requirement is imposed, but that the notation on the Office Action Summary serves notice of the previous requirements for restriction and election.

Applicants note that, following the Restriction Requirement mailed October 1, 2002, claims directed to, among other elements, a "heregulin agonist antibody" were examined (e.g., claims 2 and 9). The election of species of July 30, 2003 was directed to election of a "single disclosed species for prosecution on the merits" and noted that "[u]pon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species." Thus, Applicants respectfully submit that, upon the

allowance of a generic claim, the claimed invention, other species, including heregulin agonist antibodies and fragments, should be examined and, it is believed, allowed.

The Rejections of Claims 1-8, 10, 12, 14-17, and 19-21 under 35 U.S.C. §112

Claims 1-8, 10, 12, 14-17, and 19-21 stand rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement, the Examiner suggesting that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner discusses variants and fragments, suggesting that the claims may be directed to a great number of variants, and suggesting that the length of claimed fragments may not be sufficiently described in the claims.

However, as amended, independent claims 1, 14, and 16 are directed to only a finite number of variants, all of which variants are ligands which, when present at an effective amount, activate HER2 and/or HER3 receptors; and all of which variants have at least 80% amino acid sequence identity with the corresponding heregulin sequence. In addition, as noted by the Examiner, the specification and claims recite numerous specific amino acid residues and specific locations within the disclosed sequences where substitutions, deletions and insertions may be made. Such specific disclosure demonstrates that the inventors had possession of the claimed invention at the time the application was filed.

Independent claims 1, 14, and 16 are also directed to only a finite number of fragments, all of which fragments are ligands which, when present at an effective amount, activate HER2 and/or HER3 receptors; and all of which fragments comprise amino acids numbered 226 to 266 of the corresponding heregulin sequence. Applicants note that the claims, as originally presented and now, as amended, required

and still require that the ligands activate HER2 and/or HER3 receptors. Thus, since a single amino acid would not be expected to activate HER2 and/or HER3 receptors, the Examiner's concern that a single amino acid might be regarded as a "fragment" is seen to be unfounded.

Thus, the variants and fragments within the claims are identified by functional, quantitative, and sequence criteria which sufficiently describe the heregulin ligands of the claimed methods so as to convey to one skilled in the relevant art that Applicants had possession of the claimed invention at the time the application was filed.

Accordingly, Applicant respectfully submits that the rejections to Claims 1-8, 10, 12, 14-17, and 19-21 as allegedly failing to be supported by sufficient written description in the specification under 35 U.S.C. §112, first paragraph are overcome.

The Rejections of Claims 1, 3-8, 10, 12, 14, and 16 under 35 U.S.C. §102(e)

Claims 1, 3-8, 10, 12, 14, and 16 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 6,017,886 to Carnahan (hereafter "Carnahan"). Carnahan discusses a hybrid peptide (Carnahan SEQ ID NO: 1, shown in Fig. 1 and listed at column 2, lines 5-10 of that reference) and its effects. Carnahan also presents data from experiments on young rat utricular sensory epithelial cells treated with a variety of compounds, including recombinant rat NDFα2, recombinant human NDFα2, and recombinant human NDFβ1 (column 9, lines 55-60).

Anticipation under 35 U.S.C. § 102 requires that "every element of the claimed invention be identically shown in a single reference." (*In re Bond*, 910 F.2d 831,832 (Fed. Cir. 1990).

Applicants respectfully note that the activating ligands of claims 1, 3-8, 10, 12, 14, and 16 are selected from heregulin-β2, -β2-like, -β3, γ; specific variants and fragments of these heregulins and of heregulin-α and heregulin-β1; and heregulin agonist antibodies and antibody fragments. The variants of the claimed methods all

have at least 80% amino acid sequence identity with the corresponding heregulin sequence, and the fragments all must comprise amino acids numbered 226 to 266 of the corresponding heregulin sequence.

Carnahan does not discuss any of the above HER2 and/or HER3 receptor-activating ligands. For example, Applicants note that claimed fragments comprise amino acids numbered 226 to 266 of the corresponding heregulin sequence; however, the Carnahan hybrid α and β polypeptide does not include amino acids numbered 226 to 266 of heregulin α or of heregulin β. The activating ligands of the present claims do not include the Carnahan hybrid peptide, nor do they include recombinant rat or human NDFα2 peptides nor recombinant human NDFβ1 peptides discussed by Carnahan.

The subject matter of claims 1, 3-8, 10, 12, 14, and 16 being directed to activating ligands not discussed in Carnahan, Applicants respectfully submit that these claims are not anticipated by Carnahan. Accordingly, Applicants respectfully submit that the rejection of claims 1, 3-8, 10, 12, 14, and 16 under 35 U.S.C. § 102(e) should be withdrawn.

The Rejection of Claim 9 under 35 U.S.C. §103(a)

Claim 9 stands rejected under 35 U.S.C. §103(a) as allegedly obvious over Carnahan in view of U.S. Patent 5,587,458 to King (hereafter, "King").

In order to establish a prima facie case of obviousness, there must be 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Carnahan is presented as discussing a method of stimulating inner ear cell growth using a (hybrid) heregulin polypeptide. The Examiner notes that Carnahan "does not teach the use of an agonist antibody" (Office Action mailed July 19, 2006, page 6, paragraph 11). The Examiner presents King as teaching the construction and use of antibodies that bind and activate erbB2 (HER2), referring to the Abstract of the King reference.

However, inspection of that Abstract does not provide any disclosure or suggestion that an anti-Erb2 antibody might be able to *activate* erbB2. As seen in the Abstract, reproduced below, neither of the words "activate" and "agonist" appear in the Abstract of King:

> "The present invention relates to novel antibodies, in particular monoclonal and single chain antibodies derived therefrom which specifically bind to erbB-2, as well as diagnostic and therapeutic uses thereof. The present invention also relates to a combination of at least two erbB-2 specific antibodies which are capable of preventing and treating human malignancies wherein the malignant cells overexpress $gp185^{erbB-2}$. The monoclonal antibodies of the combination preferably recognize different epitopes of the gp185 expression product of erbB-2, therefore, the antibodies do not cross react with each other. Preferably, the combination will provide for synergistic decrease in the expression of the erbB-2 gene product."

Not only does the King Abstract fail to provide support for the Examiner's contention that "King *et al.* teach (throughout) the construction and use of antibodies that bind and <u>*activate*</u> erbB2" (emphasis added) but the specification of the King patent also fails to support the contention that King teaches activating antibodies suitable for use in the present invention.

The single use in King of the word "agonist" occurs in a paragraph (column 11, lines 20-28) directed to killing human cancer cells that over-express erbB-2. There is

no discussion of hair cells, nor of inducing hair cell generation or inner ear-supporting cell growth, or any of the other objects of the present claimed invention. More importantly, King teaches that their antibodies are suitable for killing human cancer cells overexpressing erbB-2.

Applicants note that King is directed to methods and compositions for *killing* cells; Carnahan is directed to methods and compositions for *growing* cells. Thus, being directed to *killing* cells, King is directed to a goal that is *directly opposite* to the goal of Carnahan (which discusses artificial peptides for stimulating cell growth); and being directed to *cancer cells*, King is directed to an entirely different class of cells than Carnahan (which is directed to normal inner ear cells).

Thus, being directed to different arts, different cell types, and diametrically opposed goals, there is no suggestion or motivation in King to be combined with Carnahan. Being so opposed, and being directed to different ends, there is no reasonable expectation of success for such a combination, were it to be made. Moreover, since the two references are directed to such different, and opposed, ends, it appears that the only source for motivating such a combination would come from impermissible hindsight. As stated by the Federal Circuit, "Combining prior art references without evidence of such a suggestion, teaching or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight." *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999). The Federal circuit has also stated that "In determining obviousness, the invention must be considered as a whole without the benefit of hindsight, and the claims must be considered in their entirety." *Rockwell International Corp. v. United States*, 147 F.3d 1358, 47 USPQ2d 1027 (Fed. Cir. 1998)

Since the cited references provide no motivation to combine the cited references to provide the claimed invention, nor any reasonable expectation of success were the references to be so combined, applicants respectfully submit that claim 9 is not made

obvious by the Carnahan in view of King. Accordingly, Applicants respectfully submit that the rejection of Claim 9 under 35 U.S.C. §103(a) is overcome.

The Rejection of Claim 11 under 35 U.S.C. §103(a)

Claim 11 stands rejected under 35 U.S.C. §103(a) as allegedly obvious over Carnahan in view of Carraway *et al.*, J. Biol. Chem. 269(19):14303-14306 (1994) (hereafter, "Carraway").

As discussed above, Carnahan is presented as discussing a method of stimulating inner ear cell growth using a (hybrid) heregulin polypeptide. The Examiner presents Carraway as providing rHRG-β1-177-244, "which is not specifically taught in the Carnahan patent" (page 7, lines 1-2 of the Office action mailed July 19, 2006).

However, Carraway provides no suggestion or motivation to use rHRG-β1-177-244 on inner ear cells; and Carnahan provides no suggestion or motivation to use a truncated portion of a recombinant β1 heregulin, alone and without linkage to a different heregulin sequence as well, in treatments of inner ear hair cells. In fact, there is not such suggestion or motivation in the cited references.

It appears that the Examiner feels that it would have been obvious to try the combination of Carnahan and Carraway. However, suggesting that it might have been obvious to try the claimed combination does not provide a case for obviousness. As stated by the Federal Circuit, "[O]bvious to try is not the standard." *Ecolochem, Inc. v. Southern California Edison Co.,* 227 F.3d 1361, 56 USPQ2d 1065 (Fed Cir. 2000) and "[W]e have consistently held that 'obvious to try' is not to be equated with obviousness under 35 USC 103." *Gillette Co. v. S. C. Johnson & Son, Inc.*, 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1997).

Lacking any suggestion or motivation to be combined, the cited references also fail to provide a reasonable expectation of success. Carnahan discusses hybrid artificial peptides that include sequences taken from different heregulins. However,

Carraway discusses rHRG-β1-177-244, which is derived from only a single heregulin. Canranhan's hybrid suggests that multiple sources of amino acid sequence might be required, yet Carraway has only one such source. Thus, the cited references teach away from the claimed invention, and provide no reasonable expectation of success that the rHRG-β1-177-244 polypeptide might be able to stimulate inner ear cell growth.

Accordingly, the cited references lacking any motivation or suggestion to be combined to provide the invention of claim 11, and lacking any reasonable expectation of success for such a combination, Applicants respectfully submit that the rejection of Claim 11 under 35 U.S.C. §103(a) is overcome.

CONCLUSION

In view of the foregoing, it is respectfully submitted that all claims in the present application stand in condition for allowance. Applicant respectfully requests reconsideration and allowance of all claims. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** referencing Attorney's Docket No. **39766-0035 C1**.

Respectfully submitted,

Date: September 22, 2006

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